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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HILL, KEVIN KAI	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/511,656	**Applicant(s)** SCHULTE ET AL.	
	Examiner KEVIN K. HILL	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 March 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *2-20,24,26-28,31,46,48-53 and 55-58*.
   Claim(s) withdrawn from consideration: *14-18 and 55*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
    See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Kevin K. Hill/
Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because: the claims stand rejected for reasons of record. Claims 2-13, 19-20, 24, 26-28, 31, 46, 48, 50 and 56-58 stand rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by King (U.S. 2002/0165158).
Applicant argues that the Office has misinterpreted the claims per the recitation of "consisting essentially of" (Claim 57) and "consisting of" (Claim 58).
Applicant's argument(s) has been fully considered, but is not persuasive. Applicant appears to have overlooked that King discloses the nucleic acids of the invention, i.e. dsRNA [0128], may be combined with one or more suitable carriers [0126] appropriate for the route of administration [0184], wherein the carrier may be a saline [0187]. Furthermore, while King does not disclose ipsis verbis the first and second strands of the dsRNA molecule to be complementary to each other, and that the dsRNA consists of 21 to 23 nucleotides, Applicant appears to have overlooked that King cites [0129] Elbashir et al (Nature 411(6836):494-498, 2001) who taught the gene-silencing effects of dsRNA consisting of 21 to 23 nucleotides in which the first and second strands of the dsRNA molecule to be complementary to each other (Figure 1). Thus, at the time of the instantly claimed invention, those of ordinary skill in the art would have understood the King disclosure to read upon a composition consisting/consisting essentially of saline and dsRNA molecules consisting of 21 to 23 nucleotides in which the first and second strands of the dsRNA molecule are complementary to each other.

Applicant argues that the King reference fails to disclose a method where the dsRNA is trafficked across the blood-brain or blood-retina barrier.
Applicant's argument(s) has been fully considered, but is not persuasive. As a first matter, the claimed method requires only the step of parenteral administration of the pharmaceutical composition. King discloses the instantly claimed pharmaceutical composition (discussed above) and the step of administering the pharmaceutical composition parenterally [0184]. Thus, King anticipates the claimed method step. With respect to the intended effect, such is considered an inherent result that, literally, naturally flows from the biology and anatomy of the organism. Furthermore, King discloses that the preferred target tissue embodiment is a retinal tissue [0009], which is reasonably interpreted to read upon "across said blood-brain or blood-retina barrier".

Applicant argues that the King reference fails to disclose a naked dsRNA molecule. Applicant continues to argue that the Office misinterprets the term "naked" in the context of the composition comprising the dsRNA.
Applicant's argument(s) has been fully considered, but is not persuasive. During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." >The Federal Circuit's en banc decision in Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) expressly recognized that the USPTO employs the "broadest reasonable interpretation" standard:
The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). Indeed, the rules of the PTO require that application claims must "conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 CFR 1.75(d)(1).
In the instant case, the specification discloses that a preferred embodiment of the method is to administer the pharmaceutical composition comprising a naked dsRNA by a suitable carrier (pg 14, lines 1-5), whereby "such a carrier can be a micellar structure, preferably a liposome" (pg 13, lines 4-5). The Examiner notes that the working examples fail to disclose the carrier used to administer the dsRNA molecules with which Applicant achieved the post-transcriptional gene silencing. Thus, in light of the disclosure, the broadest reasonable interpretation of the instant claims reasonably embraces "a composition comprising" a carrier vehicle, e.g. micelle or liposome, encapsulating naked dsRNA molecules.
Furthermore, Applicant appears to have overlooked that King discloses the nucleic acids of the invention, i.e. dsRNA [0128], may be combined with one or more suitable carriers [0126] appropriate for the route of administration [0184], wherein the carrier may be saline [0187], instead of a micelle or liposome.

Applicant argues that the Examiner has incorrectly cited page 14, lines 1-5 of the specification for support regarding the interpretation of "naked".
Applicant's argument(s) has been fully considered, but is not persuasive. Applicant is respectfully encouraged to continue reading the Examiner's sentence in the prior Office Action (pg 5), noting reference to page 13, lines 4-5, of the specification.

Applicant argues that the King reference fails to discuss or suggest an inner segement of the eye ball (Claim 8).
Applicant's argument(s) has been fully considered, but is not persuasive. Such is considered an untimely argument, as Applicant failed to assert this position per the King reference earlier in prosecution, e.g. the responses filed July 24, 2008 and February 13, 2009. King discloses that the preferred target tissue embodiment is a retinal tissue [0009], which is reasonably interpreted to read upon cells or tissues of an inner segment of the eyeball, absent evidence to the contrary.

Applicant argues that the King reference fails to discuss or suggest a dsRNA molecule that is between 21 and 22 nucleotides in length (Claim 13).
Applicant's argument(s) has been fully considered, but is not persuasive. Applicant appears to have overlooked that King cites [0129] Elbashir et al (Nature 411(6836):494-498, 2001) who taught the gene-silencing effects of dsRNA that is between 21 and 22 nucleotides in length. Thus, at the time of the instantly claimed invention, those of ordinary skill in the art would have understood the King disclosure to read upon dsRNA molecules that are between 21 and 22 nucleotides in length.

Applicant argues that the King reference fails to discuss or sugges a dsRNA that contains two symmetrical 3' overhangs of two nucleotides in length (Claim 48). Applicant appears to have overlooked that King cites [0129] Elbashir et al (Nature 411(6836):494-498, 2001) who taught the gene-silencing effects of dsRNA containing two symmetrical 3' overhangs of two nucleotides in length. Thus, at the time of the instantly claimed invention, those of ordinary skill in the art would have understood the King disclosure to read upon dsRNA molecules containing two symmetrical 3' overhangs of two nucleotides in length.

Claims 2-13, 19-20, 24, 26-28, 31, 46, 48-53 and 56-58 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al (U.S. Patent No. 5,814,620) in view of LaFleur et al (U.S. 6,433,145 B1) and Tuschl et al (U.S. 2002/0086356 A1).

Applicant argues that the combination of references does not yield a composition comprising naked dsRNA.
Applicant's argument(s) has been fully considered, but is not persuasive. As a first matter, the specification discloses that a preferred embodiment of the method is to administer the pharmaceutical composition comprising a naked dsRNA by a suitable carrier (pg 14, lines 1-5), whereby "such a carrier can be a micellar structure, preferably a liposome" (pg 13, lines 4-5). The Examiner notes that the working examples fail to disclose the carrier used to administer the dsRNA molecules with which Applicant achieved the post-transcriptional gene silencing. Thus, in light of the disclosure, the broadest reasonable interpretation of the instant claims reasonably embraces "a composition comprising" a carrier vehicle, e.g. micelle or liposome, encapsulating naked dsRNA molecules.
As a second matter, Applicant appears to have overlooked that Robinson et al disclose the oligonucleotides may be formulated with a pharmaceutically acceptable carrier well known in the art (col. 8, lines 54-61), i.e. physiological saline (col. 10, lines 11-12), and disclose formulating a composition consisting essentially of a gene-silencing oligonucleotide and phosphate-buffered saline (Example 2) or a balanced salt solution (Example 3).

Applicant argues that Examples 2 and 3 of Robinson describe the administration of an antisense oligonucleotide, which is a single-stranded oligonucleotide.Single-stranded RNA molecules and dsRNA molecules are not equivalents and the Office has provided no evidence as to why they would be considered equivalent by one of skill in the art. Therefore, the Office's conclusion that it was "routine" to formulate a naked dsRNA composition is not supported by the cited references.
Applicant's argument(s) has been fully considered, but is not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, La Fleur et al disclosed the functional equivalency of single- and double-stranded gene-silencing oligonucleotides (col. 9, line 52; col. 18, lines 30-40; col. 141, lines 20-23). Similarly, Tuschl et al disclosed the functional equivalency of single- and double-stranded gene-silencing oligonucleotides [0054-55]. Thus, it is unclear what Applicant considers to NOT be "routine" to formulate a naked dsRNA composition with saline as per the general knowledge of those of ordinary skill in the art at the time of the instantly asserted invention and the teachings of the cited references.

Applicant argues that the Office has failed to show that one of ordinary skill in the art would have had a reasonable expectation of success performing the claimed method with naked dsRNA.
Applicant's argument(s) has been fully considered, but is not persuasive. Applicant appears to have overlooked that Robinson et al disclose that in diseases concerning blood vessels, e.g. diabetic retinopathy, the vessels are abnormal and leaky, and thus the problem of passage through the blood brain barrier may not be a problem. Therefore, systemic delivery, i.e. intravenous injection (col. 9, line 65), may prove efficacious (col. 11, lines 15-19). Thus, at the time of the instantly asserted invention, those of ordinary skill in the art possessed a reasonable expectation of success that naked dsRNA could cross the blood-brain or blood-retina barrier when administered parenterally to an organism.